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TRAINING BASIC SCIENTISTS TO BRIDGE THE GAP BETWEEN BASIC SCIENCE AND ITS APPLICATION TO HUMAN DISEASE

INCREASINGLY, society demands that longstanding disease-related problems be solved, but who will solve them? The opportunities are greater than in the past because of the great conceptual and technical advances in basic biologic science. There is every indication that such advances will continue to develop at an increasing rate. However, as science becomes more complicated, clinical scientists have greater difficulty in applying these advances to disease, and basic scientists are needed. The complexity of disease-related problems forms a spectrum. Many problems are so complex they exceed the ability of the traditional clinical scientist to deal with them; others are less complex but necessitate collaboration between clinical and basic scientists. Unfortunately, most basic scientists have little knowledge of pathobiology or clinical medicine. Because most clinical scientists can no longer be completely competent as basic scientists, basic scientists must learn enough pathobiology to attack any disease-related problems that are waiting to be solved.

Concern about the supply of research physicians is reaching crisis proportions.[1-3] The factors responsible for the steady decline in the number of physician-scientists include the financial indebtedness of medical graduates and increasing financial pressures to earn money in practice, lengthened periods of postgraduate training for specialty certification, decreased emulation of the physician-scientist professor as a role model, uncertain long-term institutional support, and increasing competition for research funding. Competition for research grants applies to Ph.D. as well as M.D. graduates; however, there has been a progressive decline in the proportion of research grants awarded by the National Institutes of Health (NIH) to physician-scientists. In 1970, 37 percent of the NIH grantees had an M.D. degree; the proportion decreased steadily to 26 percent by 1987. In comparison, 57 percent of the 1970 NIH grantees had Ph.D. degrees, and the percentage increased to 64 percent by 1987 (Sherman CR, NIH: personal communication).

One reason clinical investigators find it difficult to remain scientifically competitive is the inadequacy of their postgraduate training in medical research. The goal of NIH-supported training programs is to provide sufficient training in research for physicians to become independent scientists and compete successfully for research funding. Of the NIH-supported trainees in medical research who began training in 1982 or 1983, only 20 percent submitted proposals for research grants to NIH by 1988 (Sherman CR, NIH: personal communication). Few medical-specialty training programs include obligatory courses in the basic sciences, and basic scientists infrequently serve as preceptors.

Many programs have been created to bridge the widening gap between advances in basic biology and their application to human disease. Most notable are combined-degree (M.D.–Ph.D.) programs, the NIH program for physician-scientists, and foundation programs that are directed at students at every academic level. However, these programs all share a premise and an objective. The premise is that "biomedical research is tightly linked to physician manpower."[1] The objective is to recreate the "golden era" of the 1950s and 1960s, when an academic physician could be a "triple threat" — clinician, teacher, and biomedical scientist. At present, this objective is not as enthusiastically sought or as frequently attained. The chief reason is that each component has become a full-time job, largely because of the increasing complexity of medical practice, the growing demands of teaching, and the rapid pace of biomedical research.

Should we direct efforts exclusively to recreating the triple-threat medical academician of the past? Are we missing other opportunities to bridge the gap between biologic science and medicine? I believe that the answer is no to the first question and yes to the second.

Almost every basic-science department in our medical schools has a graduate program. There is usually no difference between research activities and graduate programs in basic-science departments in medical schools and those in universities. Graduate students in medical schools spend approximately six years studying literally in the shadows of major medical centers. At the outset of their training, many graduate students are interested in human disease and health-related research. I interviewed 51 graduate students in the basic-science departments of medical schools; 39 stated that an interest in research related to human disease was an important factor in their decision to enter a basic-science program in a medical school rather than in a university. At the conclusion of their training, however, graduate students rarely understand what takes place in clinical departments, and

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their interest in pathobiology has largely disappeared. The major reasons are that few graduate programs teach pathobiology, and many thesis advisers in basic-science departments have little interest in clinical problems. Occasionally, basic-science faculty members express antiphysician attitudes, and students acquire them. For these reasons, it is not surprising that most graduates with Ph.D.s seek careers in academia or industry and do not seriously consider biomedical research in clinical departments. In addition, appointments in a clinical department are often considered to confer second-class citizenship on a basic scientist, mainly because scientific independence and academic tenure are frequently restricted. Consequently, as one graduate student said, "You work for, not with, a physician."

I believe that graduate students, Ph.D. postdoctoral fellows, and thesis advisers can learn sufficient pathobiology to be able to work with physicians rather than for them. To this end, we created a novel course in pathobiology for basic scientists at the Tufts University School of Medicine four years ago. The course has been completed by 54 graduate students, 7 postdoctoral fellows, and 5 faculty members. It is based on an analysis of 20 major human diseases. The students study gross and microscopic pathology, observe major diagnostic procedures (e.g., CT scanning, magnetic resonance imaging, nuclear magnetic resonance, and cardiac catheterization) and specialized patient care activities (e.g., transplantation and dialysis), and participate in presentations of patients. These activities are accompanied by a detailed analysis of the major biologic processes involved in each disease. Table 1 shows representative diseases that have been considered to date, with the associated basic biologic processes. It is surprising but reassuring that our objectives can be attained in a one-semester course that meets only twice weekly for 150 minutes per week.

To avoid overcrowding in the clinical activities, attendance is limited to 15 participants. Students or fellows from any graduate program in basic science at our school are accepted; approximately one third are first-year students.

The format is best illustrated by an example. For the first week, the topic is liver failure and regeneration, and its counterpart in basic biology is growth control. Students meet in the Pathology Department with an experienced pathologist and the course director, who is a physician-scientist. A few questions usually reveal that the students have little knowledge of the anatomy or function of the liver and cannot describe inflammation, necrosis, or fibrosis accurately. CT scans, gross liver specimens, and histologic sections are examined to teach the rudimentary but essential aspects of liver function and disease. A clinically related activity follows. A suitable patient, diagnostic procedure, or type of treatment is presented and discussed. Students are given up to six selected reprints related to the topic. Two days later, the group meets with the course director and a basic-science faculty member who is an expert in the biologic process being considered. The format is Socratic: question, answer, more questions. The students consider mechanisms, hypotheses, and experimental approaches to the basic problem.

Table 1. Topics in Pathobiology Studied in the Tufts University Course.

Disease or Condition	Biologic Process
Primary cancer of the liver	DNA viruses and cancer
Osteoporosis	Mineralization
Transplantation	Immunobiology
Atherosclerosis, gallstones	Cholesterol metabolism
Inflammation	Mediators
Lysosomal diseases	Intracellular trafficking
Leukemia	Cell proliferation
Cystic fibrosis	Regulation of ion transport
Acromegaly	Hormonal control of growth
Acquired immunodeficiency syndrome	Retrovirology
Aging	Molecular and cellular mechanisms
Idiopathic thrombocytopenic purpura	Autoimmunity
Liver failure, regeneration	Growth control

Because the course has existed for only four years, there has been no long-term follow-up. Nor is it possible to prove that the course has influenced the students' choice of research area or career. Students select the course voluntarily; but it is oversubscribed, which suggests that many students in our graduate programs seek training in pathobiology. The number of Ph.D. postdoctoral fellows and faculty members who ask to take the course has also increased steadily. In 1989, eight Ph.D. postdoctoral fellows and five faculty members have made such requests. Annual questionnaires and, when possible, interviews have been conducted with most students and fellows who have taken the course. Almost all have sustained an interest in pathobiology and encouraged other colleagues to take the course. Five students indicated that the course influenced their choice of thesis research. Most important, the students realized that an academic career in a clinical department has desirable features and should not be ruled out automatically.

When research funding for physician-scientists in clinical departments declines, so do institutional allowances for indirect costs. As this process accelerates, medical centers will come under increasing pressure to restore research efforts and solve the academic problems associated with the recruitment of basic scientists into clinical departments. According to this scenario, basic scientists who have been trained in pathobiology will have an exciting opportunity for productive careers in clinical departments.

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